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POINTS TO CONSIDER IN HUMAN SOMATIC CELL THERAPY AND GENE THERAPY

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POINTS TO CONSIDER IN HUMAN SOMATIC CELL THERAPY AND GENE THERAPY (1991)

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I. Introduction

These "Points to Consider' are concerned with somatic cell therapy and gene therapy, and are intended to provide information to manufacturers engaged in the production **and** testing of products for these therapies.

These "Points" are not regulations, but rather represent issues that the Center for **Biologics** Evaluation and Research (CBER) staff believes should be considered at this time.

Because advances in biotechnology are occurring at a rapid pace, it is anticipated that this document will be updated in the future, and these 'Points" should not be regarded as being either definitive or all-inclusive. They are presented as a draft subject to further modification, and readers are invited to submit comments to the address noted at the conclusion.

A. Definitions of somatic cell therapy and gene therapy

Recently, various innovative therapies involving the ***ex vivo*** manipulation and subsequent reintroduction of somatic cells into humans have been used or proposed. Somatic cell therapy is the administration to humans of autologous, allogeneic, or xenogeneic living cells which have been manipulated or processed ***ex vivo.*** Manufacture of products for somatic cell therapy involves the ***ex vivo*** propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics. Such cellular biological products might also be used for diagnostic or preventive purposes.

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration to humans, or may be altered in vivo by gene therapy given directly to the subject. When the genetic manipulation is performed ex ***vivo*** on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a

therapeutic or prophylactic effect, or may provide a way of marking cells for later identification. This document does not discuss genetic manipulation aimed at the modification of germ cells.

B. Types of therapies

Examples of somatic cell therapies include implantation of cells as an ***in vivo*** source of a molecular species such as an enzyme, cytokine or coagulation factor; infusion of activated lymphoid cells such as lymphokine activated killer cells and tumor-infiltrating lymphocytes (addressed in a separate Points to Consider document: see list below); and implantation of manipulated cell populations, such as hepatocytes, myoblasts, or pancreatic islet cells, intended to perform a complex biological function.

Initial approaches to gene therapy have involved the alteration and administration of somatic cells. However, future techniques may include approaches such as the direct administration to patients of retroviral vectors or other forms of genetic material. The concerns described below apply regardless of the method used, though the applicable tests may be different.

Cells for therapeutic purposes may be delivered in various ways. For example, they may be infused, injected at various sites or surgically implanted in aggregated form or along with solid supports or encapsulating materials. Any matrices, fibers, beads, or other materials which are used in addition to the cells may be categorized as excipients, additional active components, or medical devices.

Because of the complexities of potential interactions with the cells and other constituents, additional components should be considered as part of the final biological product for purposes of preclinical evaluation.

C. General considerations

Biological products are often complex mixtures that cannot be completely defined. Quality control of the manufacturing process as well as the final product is necessary. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of the biological product that may not be detectable in final product testing.

For these reasons, the methods and reagents involved in the production process should be defined. Also, cell banks and key intermediates in the production process should be subject to quality control. Lot-to-lot reproducibility of both the final product and of critical materials such as vector-containing supernatants should be examined. Existing general regulations (21 CFR 210, 211, 312 and 600) may be relevant and should be consulted for guidance.

Some of the issues regarding cellular and gene therapy products overlap with those discussed in other Points to Consider documents. It is suggested that the most recent versions be reviewed. The following documents are relevant:

Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology (1985)

Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1987)

Points to Consider in the Manufacture and Testing of Monocional Antibody Products for Human Use (1987)

Points to Consider in the Collection, Processing, and Testing. of Ex- *Vivo*-Activated Mononuclear Leukocytes for Administration to Humans (1989).

The following sections indicate areas of concern and questions to be addressed by manufacturers of such products when filing applications. Initial clinical trials should be preceded by submission of data adequate to assure a reasonable degree of safety. A description of the methods used, actual data from appropriate tests, and evidence of assay validation should be included.

It may not be practical or possible to address all of the issues discussed below for a given system. In some instances, tests mentioned will be inapplicable or inappropriate, or alternative procedures may be more appropriate. The methods and procedures mentioned are suggestions: sponsors may propose alternative techniques which will be acceptable if these issues are adequately addressed. In addition, all of the information discussed below may not be necessary before clinical trials are initiated.

The points to consider suggested in this document are based in part on an assessment of the limited experience available with cell and gene therapy products and methods of production. Modifications of procedures will occur with time, and alternate control procedures will be needed. The principles included here can serve as guidance for developing these procedures.

II. Development and characterization of cell populations for administration

A. Collection of cells

The following information should be provided:

1. Cell types: The type(s) of cell to be used should be classified as autologous, allogeneic, or xenogeneic in origin. The tissue source and other relevant identifying information should be provided.

2. Donor selection criteria: Any relevant characteristics of the donor(s) should be specified, including age and sex. If animal species other than humans are used, a description should be provided of the origin, relevant genetic traits, husbandry, and health status of the herd or colony.

As stated in the "Points to Consider in the Collection, Processing, and Testing of Ex-Vivo-Activated Mononuclear Leukocytes for Administration to Humans," as a minimum, allogeneic donors should meet the standards for blood donors (21 CFR **640.3),** the testing and acceptance procedures should be described, and any deviations should be justified. Where applicable, additional Public Health Service recommendations regarding organ and tissue donors should be incorporated. Exclusion criteria should focus on the presence or likelihood of infection by HIV-1 and HIV-2, hepatitis B and C viruses, HTLV-1, and other infectious agents. Serological, diagnostic, and clinical history data to be obtained from donors should be specified. Provision for follow-up of donors will be appropriate in some cases and methods of obtaining donor data and record keeping should be thoroughly described.

3. Tissue typing: If allogeneic donors are to be used, typing for polymorphisms such as blood type should be included when appropriate. The importance of matching for histocompatibility antigens (HLA class I and/or II, and perhaps minor antigens in some cases) between donor and recipient should be addressed, and typing procedures and acceptance criteria provided.

Should it be indicated or necessary to use mixtures of cells from multiple donors, special attention should be paid to possible cell interactions that could result in immune responses or other changes that might alter the performance of the cells. Characterization of multiple-donor cell mixtures may be problematic.

4. Procedures: The procedures for the collection of cells, including the location of the facility, and any devices or materials used, should be submitted.

B. Cell culture procedures

1. Quality control procedures: In general, cell culture operations should be carefully managed in terms of quality of materials, manufacturing controls, and equipment validation and monitoring. See I, C, General Considerations.

2. Culture media: Acceptance criteria should be established for all media and components, including validation of serum additives and growth factors, as well as verification of freedom from adventitious agents. Records should be kept detailing the components used in the culture media, including their sources and lot numbers. Medium components which have the potential to cause sensitization, for example certain animal sera, certain antibiotics (penicillin), selected proteins, and blood group substances, should be avoided. For growth factors, measures of identity, purity, and potency should be established to assure the reproducibility of cell culture characteristics. More detailed discussions of specifications for medium components and biologicals added to cultures are presented in the "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" and the "Points to Consider in the Collection, Processing, and Testing of *Ex-Vivo*-activated Mononuclear Leukocytes for Administration to Humans."

3. Adventitious agents in cell cultures: Documentation should be provided that cells are handled, propagated, and subjected to laboratory procedures under conditions designed to minimize contamination with adventitious agents. During long term culturing, cells should be tested periodically for contamination. Testing should ensure that cells are free of bacteria. yeast, mold, mycoplasma, and adventitious viruses. For a discussion of adventitious agent testing and details regarding virus testing, the

"Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" should be consulted. A copy of "Recommended test procedures for mycoplasmas' can be obtained from the Director, CBER.

4. Monitoring of cell identity and heterogeneity: Both manufacturing and testing procedures should be implemented which ensure the control of cell cultures with regard to identity and heterogeneity.

Cell culturing practices and facilities should be designed to avoid contamination of one cell culture with another. Suggestions can be found in the Good Manufacturing Practices regulations (21 CFR 210, 211, 610.11 and 610.18).

During cell culturing, extensive drift in the properties of a cell population, or overgrowth by a different cell type originally present in low numbers, may occur. To detect such changes, cell identity should be assessed quantitatively, for example, by monitoring cell surface antigens or biochemical markers. The method of identification chosen should also be able to detect contamination or replacement by other cells in use in the facility. Acceptable limits for culture composition should be defined. Quantitative assays of functional potency may sometimes provide a method for population phenotyping. The desired function should be monitored when the cells are subjected to manipulation, and the tests carried out periodically to assure that the desired trait is retained. Identity testing should in some cases include verification of donor-recipient matching and immunological phenotyping.

5. Tests of particular product(s) biosynthesized by the cells and required for the therapeutic effect: If the intended therapeutic effect is based on a particular molecular species synthesized by the cells, enough structural and biological information should be provided to show that an appropriate and biologically active form is present.

6. Culture longevity: The essential characteristics of the cultured cell population (phenotypic markers such as cell surface antigens, functional properties, activity in bioassays, as appropriate) should be defined, and the stability of these characteristics established with respect to time in culture. This profile should be used to define the limits of the culture period.

C. Cell banking procedures

When cell banks are used, the "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" should be consulted for a discussion of cell banking practices for master cell banks and manufacturer's working cell banks. In addition, 21 CFR 610.18 may be applicable. The cell bank system used should be described and should include:

1. The origin and history of the cells.

2. Procedures: The procedure for freezing and for recovering the cells should be described. Components used (such as DMSO or glycerol) should be described, along with information detailing their removal from the cell preparation and an assessment of their toxicity. The number of vials typically. preserved in a single lot and the storage conditions should be specified.

3. Tests on thawed cells: Tests of viability, cell identity, and function should be repeated after thawing and/or expansion. The yield of viable cells and of quantitative functional equivalents should be compared to those values before freezing. Steriiity should be confirmed using aliquots of the frozen cells.

4. Expiration dating: Product development plans should include accumulation of data demonstrating how long and under what conditions the cells can remain frozen and still be acceptably active when thawed.

Management of cell banks for gene therapy: Cell banking systems should be developed and maintained for each type of cell line used in manufacture, including the packaging cell line used for the production of batches of the recombinant vector and, if appropriate, the cell line that is transduced to form the final product.

D. Materials used *in* vitro for cell manipulation and growth

Materials used during the *in* vitro manipulation procedures, for example antibodies, serum, protein A, toxins, antibiotics, other chemicals, or solid supports such as beads, should be indicated and specifications for these materials provided. Limits for their concentrations in the final product, the methods used to remove them, and the results of quantitative testing (including a description of methods and sensitivity) to show the effectiveness of their removal should be given. Some added components, by virtue of binding or uptake, may be present in measurable amounts when the cells are administered. In such cases, consideration should be given to assessing toxicity of these components in animals or other appropriate systems.

E. Molecular genetic characterization of constructs for gene therapy .

1. Characterization of gene construct: The sequence of the gene and its flanking sequences in the vector being introduced into the cells should be provided, along with information about its derivation. Complete descriptions of any vectors, helper viruses, and producer cell lines used for preparation of the final construct should be given, including their derivation, characterization, conditions for growth, and the materials and methods used. Known regulatory elements such as promoters or enhancers contained within the construct should be identified. Stability of the vector with respect to potential for rearrangement, recombination, and mutation should be assessed, both under the conditions actually employed and after prolonged culture to permit emergence of

variants from the packaging cell line and possibly from preclinical cell preparations similar to the final product. If genetic elements are incorporated as safety measures to permit recall/inactivation of cells after administration to the patient, they should be described, and data evaluating the safety and effectiveness of the cell inactivation system submitted.

For product control purposes, each distinct vector is considered a different product, and should be fully characterized and tested for safety.

2. Methods of vector insertion and implications: Recombinant sequences may be introduced into cells by site-specific recombination techniques or by methods that result in random insertion, e.g. retroviral vectors. If site-specific gene insertion is used, the segment inserted and adjacent sequences should be characterized to demonstrate that the insertion occurred as expected. If random gene insertion techniques are used, tests should be performed on representative preparations to determine the average number of copies inserted per cell, and whether the integration is chromosomal or extrachromosomal.

3. Packaging 'cell lines: Packaging cell lines are often used to produce vector-containing supernatants for transduction of cells with exogenous genes. In such cases, the origin, history, and biological properties of the packaging cell line should be described. The structure and stability of the genes responsible for viral packaging should be characterized along with any safety features of the line. A master cell bank of the vector-containing packaging cells should be characterized and subjected to quality control (see Part II, C). The permissible number of passages or population doublings between the master cell bank and production cells used to make working vector supernatants should be established, and should reflect both the transducing ability of the supernatants and the absence of replication-competent virus. Each lot of vector-containing supernatant for use in transduction should also be tested for transducing ability and for the absence of replication-competent virus.

III. Preclinical testing

A. Safety evaluation

Some combination of animal model studies and *in vitro* testing that will be informative about product safety should be performed. Safety testing should cover a dose range that includes and exceeds the doses to be used in humans.

1. Growth factor-dependence: In cell cultures dependent on exogenous- growth factors, growth patterns should be monitored. If a cell line exhibits uncontrolled growth, and in particular, if a cell line was formerly factor-dependent and becomes factor-independent, the cells should not be used. If transformed xenogeneic cell lines are to be encapsulated and used *in vivo,* their use and control will probably involve special considerations not addressed in this document.

2. Tumorigenicity: Tests of tumorigenicity will be appropriate when the manipulation could alter the normal growth pattern or the regulation of expression of a cellular oncogene, *trans-*acting factor, growth factor, or growth factor receptor. Alterations of any of these could affect the growth properties of the implanted cells or of other cells in the recipient. For example, this concern could arise when cells are propagated over long periods of time *in* vitro or when cells are manipulated genetically.

Tumorigenicity testing is commonly done using suitable animal models such as nude mice or immunosuppressed animals. A detailed description of tumorigenicity testing is found in the "Points to Consider on Cell Lines Used for Production of Biologicals".

If non-malignant cells for therapeutic use are prepared from human tumor tissue, residual tumor cells in the cell preparation should be quantitated and the completeness of tumor cell removal from the cell population should be documented before reintroduction into the patient.

3. Gene insertion:

a. Viral replication: Proposed retroviral vector preparations should be tested for replicating virus, and the limits of detection established 'for the assays used. Producer cell lines should be tested for replicating virus after culturing cells beyond the normal culture period used for production to favor emergence of any competent virus. Available evidence should be provided from the genetically modified cell population demonstrating, by a sensitive method, that any viral vector used in its production, mutants derived from it, or portions of it which may have recombined with endogenous retroviral sequences, are not reproducing.

b. Insert stability: The stability of the inserted genetic material should be characterized, for example, by tests for the integrity of the insert itself or the RNA transcribed from it, with respect to 'mutations, recombinations or rearrangements. Note that sequence changes may occur at any time and are not ruled out by testing at a single point in time. Data should be provided describing the fraction of cells in the population containing the insert and the length of time the insert is retained. The study of growth prolonged beyond the normal culture period can be used to define the limits of the system's stability.

c. Function of the inserted gene: The appropriate functioning of the inserted gene should be established. The possibility of poorly regulated cell function or gene expression (under- or overproduction of biologically active substances) should be considered in the safety evaluation. For key products made by the cells, the level of expression should be evaluated for risk potential by comparison to the level produced by normal cells or by the same patient's cells prior to manipulation. Stability of function over time should also be demonstrated by quantitative measures of biological activity.

d. Insertional mutagenesis: Interruption of the function of a cellular gene by insertional mutagenesis may affect readily observable characteristics of the cell. If changes occur in cell morphology, growth characteristics, or biological function (e.g., interruption of expected production of a growth factor), the possibility of insertional mutagenesis should be considered.

4. *In vivo* safety testing: In some cases, preclinical animal studies can reveal adverse effects mediated by the cells or their products. Such testing can involve animal models (in some cases appropriate transgenic animals) or human cells tested in immunoincompetent animals, since immunological rejection of the cells during an animal test would limit the relevance of the test. A relevant animal species would be one whose biological response to the therapy would be expected to be related to the response in humans. For example, if the therapy were based on a human cytokine secreted by the cells, the safety test might involve an animal species possessing a receptor to which the human cytokine binds with reasonable affinity. Alternatively, an animal model which mimics the human therapeutic situation but uses cells from the same animal species might be appropriate. Animal models may be used for a variety of purposes, including evaluation of the safety and stability of vectors for gene therapy. Because of the highly experimental nature of somatic cell and gene therapy, animal testing should be designed in each case to study those safety issues that can be reasonably addressed in animals prior to testing in humans.

The interaction of administered cells or their products with other cells that are not the intended target of therapy can lead to adverse effects. Localization and potential toxicity at other sites should be considered and evaluated to the extent possible.

The complete results of all animal safety studies and any findings of adverse effects in any animal studies should be reported.

B. Efficacy evaluation

Efficacy models may be very useful. **Preclinical** studies should support a rationale for initiating investigation of the therapy in clinical trials, although evidence of efficacy is not always possible or needed before beginning such trials. Parts 3b and 3c above addressing gene insertion are relevant to the evaluation of efficacy. In some cases, the mechanism of the therapeutic effect may be unknown and some of the following may not apply. information relevant to an evaluation of efficacy includes:

1. Cell phenotype: The cell type necessary for the intended effect should be identified when possible and phenotypically characterized by a combination of morphology, cell surface markers, functional parameters, and biochemical features. The cultured cells should contain the desired cell type(s) and should be functional, as shown by available ***in vitro*** measures (for example, production of a product, cytotoxic activity, or stem cell activity).

2. Products of the cells: If the therapeutic effect is dependent upon the production of a specific factor, the identity and biological activity of the factor expressed by the cells should be established. Information about rates of synthesis and secretion of the active product, and the stability of such rates, will also be useful. Levels should be compared with levels known to be safe and physiologically effective. If there are alternative forms or cellular localization of a product, such as membrane-bound versus soluble protein, their presence and amounts should be determined.

3. ***In vivo*** testing: If an animal model is available, *in vivo* survival time of the cells should be determined. Function of the cells *in vivo* should also be assessed. If the cells must go to a particular site in order to achieve the desired effect, cell localization should be analyzed. The ability of the therapy to accomplish its intended effect should be studied in the appropriate animal model of disease, when possible.

C. Immunological concerns

The implanted cells, their product(s), or host structures modified by the action of the cells may be immunogenic or cause other immunological alterations. Animal models may not be informative about immune effects in humans, since species differ in structures expressed by the cells and immunogenicity in animal models may not reflect human responses. These effects could only be analyzed in clinical trials. However, if a relevant animal model is available, the following should be considered: antigenic differences between donor and host; immune or allergic responses to the cells or their products; antigens recognized by any such responses; effects of such responses on the safety and effectiveness of the therapy; and any evidence noted of autoimmunity or graft-versus-host reactions caused by the cells.

IV. Lot-to-lot manufacturing control and release testing

The final biological product to be administered, as well as the production process and materials used, should be subjected to quality control testing. 'The specifications to be applied to the final product and to other elements of the production process, along with the range of acceptable values for each, should be specified.

One lot of a biological product is considered to be a quantity of material that has been thoroughly mixed in a single vessel. This' concept can be applied to somatic cell and gene therapy for purposes of planning lot testing procedures. This means that each cell population, vector preparation, or other product for such therapies prepared as a unique final mixture should be subjected to appropriate lot release testing. Preparations intended solely for individual recipients differ from products prepared as large batches, and appropriate lot release criteria should be chosen to fit the practical constraints of each protocol. Lot-to-lot variation provides a measure of the reproducibility of the procedures.

A. Cell identity. Quantitative testing by phenotypic and/or biochemical assays should be used to confirm cell identity and assess heterogeneity.

B. Potency. The relevant function of the cells, if known, and/or relevant products biosynthesized by the cells should be defined and quantitated as a measure of potency.

C. Viability of the cells should be quantitated and a lower limit for acceptability established.

D. Tests should demonstrate that the cells are not contaminated with adventitious agents such as bacteria, fungi, mycoplasma, or viruses.

E. The suitability and appropriateness of methods of endotoxin testing should be considered on a case-by-case basis. The test used should be validated to show that the cell preparation does not interfere with endotoxin detection.

F. The general safety test (21 CFR 610.11) should be performed on the final product when it is prepared in large enough batches to make this test feasible. When appropriate, modified procedures may be developed.

G. Cell populations frozen for subsequent implantation. If frozen cells are thawed, perhaps expanded, and then administered to patients, lot release testing on the thawed cells is needed, and can be adapted from Part II, E on cell banking practices.

H. Live vectors. Live virus vectors intended for use as final products should be subjected to lot-by-lot testing designed to be relevant to the production system and characteristics of the vector. Procedures analogous to those used for lot-by-lot testing of live virus vaccines should be employed.

V. Additional applications: addition of radioisotopes or toxins to cell preparations

Therapeutic or diagnostic applications may be proposed involving cells which are modified by radiolabeling or pre-loading with bioactive materials such as toxins. Thus, the cell implant may be used as a delivery system not only for its own products and functions but also for other products. Similar special issues have been raised in the past by use of radiolabeled or toxin-conjugated antibodies, and are addressed in the 'Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use". Although the application to somatic cell therapies may differ, that document should be consulted.

In addition, novel safety concerns may arise related to the site of cell implantation and localization of the radionuclide or toxin, or due to metabolic properties of the cells. These should be anticipated and addressed where possible.

VI. Considerations regarding clinical trials

The use of somatic cell or gene therapy in clinical trials raises some novel concerns due to the nature of the therapeutic agents. Although a complete discussion of clinical trial design will not be presented here, some of the special concerns in cellular therapies can be highlighted. Patients should be monitored for survival of the cells, localization of implanted cells in the body, cell function, quantitation of key products made by the cells and their pharmacokinetics and biodistribution, presence of exogenous sequences inserted into the genetic material of cells, replication of viral vectors, and adverse reactions including infections related to infusion or implantation. The nature of the proposed indications and patient populations may often require long-term follow-up, in some cases for the lifetime of the recipient. Use of viral vectors may in

special cases require testing of clinical personnel or household contacts to confirm lack of infectious spread. The inclusion of children or pregnant women in such trials will raise special concerns about developmental effects.

In gene therapy, the product of the inserted gene must be considered as a potential source of immune reactions; an individual who is genetically defective for the production of a given molecular species may not be immunologically tolerant to it. Animal models may give only limited guidance as to the effects in humans. When applicable, information on testing procedures and results should be provided regarding: evidence of immune responses to the cells or their products, whether immune responses that do occur alter safety or therapeutic effectiveness;' any evidence of a graft-versus-host response and its clinical consequences; immunosuppressive regimens used with the therapy or evidence of immune suppression by the therapy; any data suggesting development of autoimmune reactions during therapy; evidence of allergic reactions to therapy; and information about attempts to identify the component responsible for any immune responses seen.

VII. Conclusion

Concerns about somatic cell and gene therapy include those common to all biological products, those applying to cell preparations, and those unique to genetic alterations. New issues are likely to emerge in the future, as experience is gained. For the present, however, the issues mentioned here should be considered by those developing biological products to be used for such therapies.